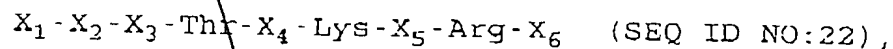


## CLAIMS

1. Use of a substance or polypeptide according to the formula



wherein

5  $X_1$  is Ala or Gly,

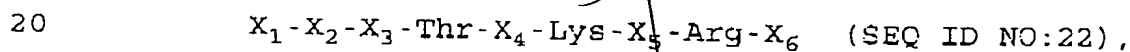
$X_2$  is Tyr or Phe,

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

10  $X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

optionally at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently substituted with a non-natural or unusual amino acid and/or the peptide is cyclized and/or the peptide is stabilized and/or the amino terminal amino acid residue is acylated and/or the carboxy terminal amino acid residue is amidated, and peptidomimetics modelled on the basis of the above formula for the preparation of a pharmaceutical composition for the reduction of TNF $\alpha$  production.

2. Use of a substance or polypeptide according to the formula



wherein

$X_1$  is Ala or Gly,

$X_2$  is Tyr or Phe,

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

25  $X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

optionally at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently substituted with a non-natural or unusual amino acid and/or the peptide is cyclized and/or the peptide is stabilized and/or the amino terminal amino acid residue is acylated and/or the carboxy terminal amino acid residue is amidated, and peptidomimetics modelled on the basis of the above formula for the preparation of a pharmaceutical composition for the prophylaxis or treatment of pancreatitis.

3. Use of a substance or polypeptide according to the formula

10  $X_1$ - $X_2$ - $X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:22),

wherein

$X_1$  is Ala or Gly,

$X_2$  is Tyr or Phe,

15  $X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

optionally at least one of  $X_1$ ,  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently substituted with a non-natural or unusual amino acid and/or the peptide is cyclized and/or the peptide is stabilized and/or the amino terminal amino acid residue is acylated and/or the carboxy terminal amino acid residue is amidated, and peptidomimetics modelled on the basis of the above formula for the preparation of a pharmaceutical composition for the prophylaxis or treatment of viral infections such as acquired immun-deficiency syndrom (AIDS) or cutaneous HPV-infection.

4. A substance or polypeptide having the formula

$X_1$ - $X_2$ - $X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:22),

30 wherein

X<sub>1</sub> is Ala or Gly,

X<sub>2</sub> is Tyr or Phe,

X<sub>3</sub>, X<sub>4</sub> and X<sub>5</sub> are independently selected from the group consisting of Met, Ile, Leu and Val; and

5 X<sub>6</sub> is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently substituted with a non-natural or unusual amino acid, said substance or polypeptide having at least one of the  
10 following properties

- 05479 534150
- a) induces inhibition of spontaneous IL-8 production by human monocytes,
  - b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),
  - 15 c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
  - d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,
  - e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
  - 20 f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
  - g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
  - 25 h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
  - i) induces the production of IL-4 by cultured normal human CD4+ T cells,
  - j) reduces the TNF $\alpha$  production in human mixed leukocyte  
30 reaction,
  - k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

5. A substance or polypeptide having the formula

$X_2$ - $X_3$ -Thr- $X_4$ -Lys- $X_5$ -Arg- $X_6$  (SEQ ID NO:21),

wherein

$X_2$  is Tyr or Phe,

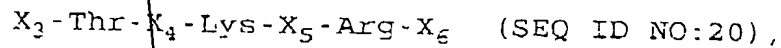
$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of  $X_2$ ,  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently substituted with a non-natural or unusual amino acid, said substance or polypeptide having at least one of the following properties

- a) induces inhibition of spontaneous IL-8 production by human monocytes,
- b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),
- c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) induces chemotactic migration of CD8+ human T lymphocytes in vitro,
- e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
- f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
- g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
- i) induces the production of IL-4 by cultured normal human CD4+ T cells,
- j) reduces the TNF $\alpha$  production in human mixed leukocyte reaction,
- k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

6. A substance or polypeptide having the formula



wherein

- 5  $X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and  $X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently  
10 substituted with a non-natural or unusual amino acid, said substance or polypeptide having at least one of the following properties

- a) induces inhibition of spontaneous IL-8 production by human monocytes,
- 15 b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),
- c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) induces chemotactic migration of CD8+ human T lymphocytes  
20 *in vitro*,
- e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
- f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
- 25 g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
- i) induces the production of IL-4 by cultured normal human  
30 CD4+ T cells,
- j) reduces the TNF $\alpha$  production in human mixed leukocyte reaction,

k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

7. A substance or polypeptide having the formula

5 Thr-X<sub>4</sub>-Lys-X<sub>5</sub>-Arg-X<sub>6</sub> (SEQ ID NO:19),

wherein

X<sub>4</sub> and X<sub>5</sub> are independently selected from the group consisting of Met, Ile, Leu and Val; and

10 X<sub>6</sub> is selected from the group consisting of Asn, Asp, Gln and Glu,

wherein at least one of X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently substituted with a non-natural or unusual amino acid, said substance or polypeptide having at least one of the following properties

- 15 a) induces inhibition of spontaneous IL-8 production by human monocytes,
- b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),
- 20 c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) induces chemotactic migration of CD8+ human T lymphocytes *in vitro*,
- e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
- 25 f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
- g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
- 30 i) induces the production of IL-4 by cultured normal human CD4+ T cells,

- j) reduces the TNF $\alpha$  production in human mixed leukocyte reaction,  
k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.

8. A substance or peptide according to any of claims 4-7 which is cyclized.

9. A substance or peptide according to any of claims 4-7 which is stabilized.

10. A substance or peptide according to any of claims 4-7 wherein the amino terminal amino acid residue is acylated.

11. A substance or peptide according to any of claims 4-7 wherein the carboxy terminal amino acid residue is amidated.

12. A peptidomimetic modelled on the basis of the formula

15  $X_1-X_2-X_3\text{-Thr-}X_4\text{-Lys-}X_5\text{-Arg-}X_6$  (SEQ ID NO:22),

wherein

$X_1$  is Ala or Gly,

$X_2$  is Tyr or Phe,

$X_3$ ,  $X_4$  and  $X_5$  are independently selected from the group consisting of Met, Ile, Leu and Val; and

$X_6$  is selected from the group consisting of Asn, Asp, Gln and Glu,

said peptidomimetics having at least one of the following properties

- 25 a) induces inhibition of spontaneous IL-8 production by human monocytes,  
b) induces inhibition of IL-1 $\beta$  induced IL-8 production by human peripheral blood mononuclear cells (PBMC),

- c) induces production of interleukin-1 receptor antagonistic protein (IRAP) by human monocytes,
- d) induces chemotactic migration of CD8+ human T lymphocytes *in vitro*,
- 5 e) desensitizes human CD8+ T cells resulting in an unresponsiveness towards rhIL-10,
- f) suppresses the chemotactic response of CD4+ T human lymphocytes towards IL-8,
- 10 g) suppresses the chemotactic response of human monocytes towards MCAF/MCP-1,
- h) inhibits class II MHC molecule expression on human monocytes stimulated by IFN- $\gamma$ ,
- i) induces the production of IL-4 by cultured normal human CD4+ T cells,
- 15 j) reduces the TNF $\alpha$  production in human mixed leukocyte reaction,
- k) downregulates TNF $\alpha$  and IL-8 production in a rabbit model of bile acid induced acute pancreatitis and reduces neutrophil infiltration in the lungs of the treated rabbits.
- 20 13. A pharmaceutical composition comprising a substance or polypeptide according to any of claims 4-12.
14. Use of a substance or polypeptide according to any of claims 4-12 for the treatment or prophylaxis of one or more of the diseases mentioned in Tables 1 and 2.
- 25 15. Use of a substance or polypeptide according to claim 4-12 for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of one or more of the diseases mentioned in Tables 1 and 2.
- 30 16. A method of treating and/or preventing one or more of the diseases mentioned in Tables 1 and 2, the method comprising administering to a patient in need thereof a therapeutically or prophylactically effective amount of a substance or polypeptide according to any of claims 4-12.

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17. Synthesis of a substance or peptide according to any of claims 4-12 by use of solid-phase peptide synthesis (SPPS), the process comprising the following steps:

- 5 a) covalently coupling the C-terminal amino acid in the form of an N- $\alpha$ -protected, optionally side chain-protected reactive derivative, either directly or by means of a suitable linker to a solid support,
- b) removing the N- $\alpha$ -protective group,
- 10 c) adding the succeeding protected amino acids according to the desired sequence in a stepwise manner,
- d) removing the side chain-protective groups if any,
- e) upon assembly of the complete peptide chain cleaving the peptide from the resin, and optionally
- 15 f) cyclizing and/or stabilizing the peptide and/or acylating the amino terminal amino acid residue and/or amidating the carboxy terminal amino acid residue.

add B1 →

add C1 →

add D4 →

add D1

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